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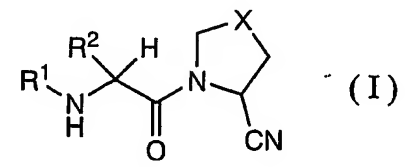
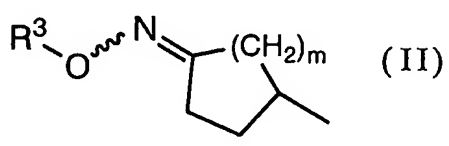
(54) Title: DPP-IV INHIBITOR



(I)



(II)

(57) Abstract: A compound of the formula (I) or a pharmaceutically acceptable s alt thereof: [wherein X is CH?2#191, O or S, R_1 is the moiety represented by the formula (II), etc.: [wherein R_3 is lower alkyl, etc., m is integer of 1 to 3], R_2 is hydrogen, etc.]. Compouund of formula (I) inhibits DPP-IV activity. They are therefore useful in the treatment of conditions mediated by DPP-IV, such as NIDDM.

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DESCRIPTION

DPP-IV INHIBITOR

TECHNICAL FIELD

This invention relates to the compounds and pharmaceutically acceptable salts thereof which inhibit dipeptidyl peptidase-IV (DPP-IV).

BACKGROUND ART

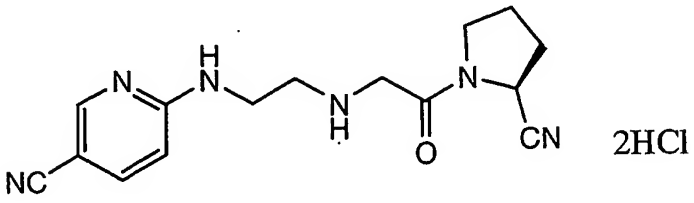
It is known that DPP-IV has various physiological functions in living body, especially has the action which inactivates Glucagon-like peptide-1 (GLP-1) by cleaving the terminal dipeptide (His-Ala). And the resultant peptide is the receptor antagonist of GLP-1 and totally reduces the activity of GLP-1.

This GLP-1 has very important role in sugar metabolism. For example, (1) GLP-1 intensifies the secretion of insulin, (2) express genes which are indispensable for the secretion of insulin, (3) stimulate proliferation of β-cell, (4) suppresses secretion of glucagon, (5) suppresses the function about secretion and motility of digestive organs (especially, peristalsis), and (6) suppresses appetite. That is, GLP-1 restricts food ingestion, postpones the process of digestion and absorption, and raised the use of the sugar in blood.

Therefore, the inhibitor of DPP-IV can maintain the activity of GLP-1, so it is expected as a medicine to treat and prevent various diseases, especially non-insulin dependent diabetes mellitus (NIDDM).

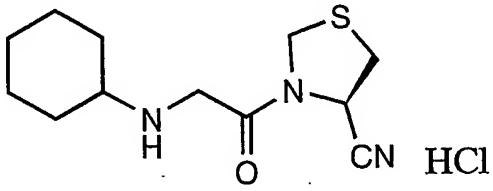
Hitherto, such inhibitors of DPP-IV are known so far.

For example, in US 6,011,155, 2-cyanopyrrolidine compounds like following are disclosed.



Pyrrolidine, 1-[[2-[(5-cyano-2-pyridinyl)amino]ethyl]amino]actyl-2-cyano, (S)-, dihydrochloride

In US 6,110,949, 4-cyanothiazolidine compounds like following are disclosed.



3-[(Cyclohexyl)amino]acetyl-4-cyano-(R)-thiazolidine monohydrochloride

DISCLOSURE OF INVENTION

Under the above situation, the inventors of this invention found that the introduction of the oxime derivative group at appropriate position of the compound results in remarkable improvement of the activity to inhibit DPP-IV. And the inventors completed this invention.

Accordingly, this invention relates to DPP-IV inhibitor. More particularly, this invention relates to DPP-IV inhibitor useful for treating and/or preventing the medical conditions mediated by DPP-IV, more particularly useful for treating and/or preventing

altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus (IDDM and NIDDM), diabetic neuropathy, nephropathy, and secondary diseases in mammals caused by diabetes mellitus.

That is, one object of this invention is to provide novel compounds and pharmaceutically acceptable salts thereof, of which activity to inhibit DPP-IV is remarkably improved against known compounds.

Another object of this invention is to provide a medicament and pharmaceutical composition containing the compound and/or pharmaceutically acceptable salts thereof as an active ingredient.

A further object of this invention is to provide an inhibitor of DPP-IV consisting of the compound and/or pharmaceutically acceptable salts thereof.

A further object of this invention is to provide a method for treating and/or preventing the medical conditions comprising to administer an effective amount of the compounds and/or pharmaceutically acceptable salts thereof.

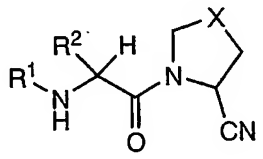
A further object of this invention is to provide a use of the compounds and pharmaceutically acceptable salts thereof as medicaments.

A further object of this invention is to provide the compounds and pharmaceutically acceptable salts thereof which are useful for the manufacture of medicaments for treating and/or preventing the medical conditions mediated by DPP-IV

A further object of this invention is to provide the commercial package comprising the pharmaceutical

composition containing the compound and a written matter associated therewith, wherein the written matter states that the compound can or should be used for preventing and/or treating the medical conditions mediated by DPP-IV.

The compounds of this invention can be represented by the following formula (I):

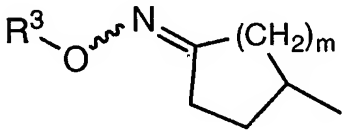


(I)

[wherein

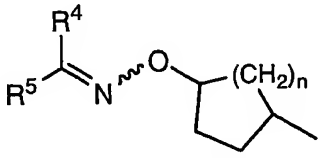
X is CH_2, O or S,

R^1 is hydrogen, lower alkyl, the moiety represented



by the formula:

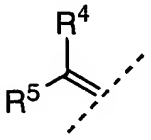
[wherein R^3 is lower alkyl, aryl (which may have 1 to 3 substituent(s) selected from the group described later), heteroaryl (which may have 1 to 3 substituent(s) selected from the group described later), aryl-(lower alkyl) (which may have 1 to 3 substituent(s) selected from the group described later on the aryl group), or heteroaryl-(lower alkyl) (which may have 1 to 3 substituent(s) selected from the group described later on the heteroaryl group), m is integer of 1 to 3], or



the moiety represented by the formula:

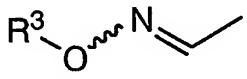
[wherein R^4 is hydrogen or lower alkyl, R^5 is lower alkyl, aryl (which may have 1 to 3 substituent(s) selected

from the group described later), or heteroaryl (which may have 1 to 3 substituent(s) selected from the group described later), or the partial structure:

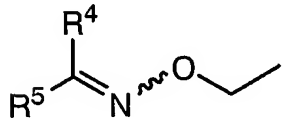


may form cycloalkyl, n is integer of 1 to 3],

R^2 is hydrogen, the moiety represented by the formula:



[wherein R^3 represents the same definition defined above], or the moiety represented by the formula:



[wherein R^4 and R^5 represent the same definition defined above],

the substituent(s) is(are) selected from the group consisting of lower alkyl, lower alkoxy, halogen, cyano, nitro, amino and hydroxy,

provided that both of R^1 and R^2 are not hydrogen at the same time; and either R^1 and R^2 is hydrogen, or when R^1 is lower alkyl, R^2 is not hydrogen.]

In the above and subsequent description of the present specification, suitable examples of the various definitions to be included within the scope of the invention are explained in detail in the following.

The term "lower" is intended to mean a group having

1 to 6 carbon atom(s), unless otherwise provided.

So, the "lower alkyl" means a straight or branched chain aliphatic hydrocarbon, such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl, hexyl, and the like, and it is preferably C1-C4 alkyl, more preferably C1-C2 alkyl, most preferably methyl.

The "aryl" means C6-C10 aromatic hydrocarbon group, such as phenyl, indenyl, naphthyl, and the like, and it is preferably phenyl. And the "aryl" may have 1 to 3 substituent(s), the number of substituent is preferably 1 or 2, more preferably 1, in case that "aryl" has plural substituents, they may be the same or different each other, but, needless to say, "aryl" may not have substituent.

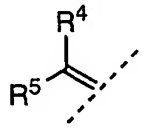
The "heteroaryl" means 5- or 6-membered aromatic heterocyclic group which contains at least one hetero atom such as nitrogen, oxygen, sulfur atom, preferably contains nitrogen atom. The "heteroaryl" may include 5-membered heteroaryl group such as pyrrolyl, imidazolyl, pyrazolyl, thienyl, furyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl; and 6-membered heteroaryl group such as pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, or the like, and is preferably 6-membered heteroaryl, more preferably pyridyl. And the "heteroaryl" may have 1 to 3 substituent(s), the number of substituent is preferably 1 or 2, more preferably 1, in case that "heteroaryl" has plural substituents, they may be the same or different each other, but, needless to say, "heteroaryl" may not have substituent.

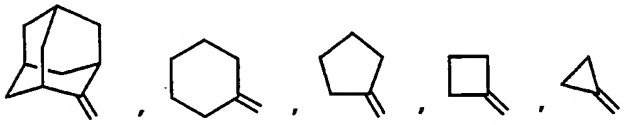
The "aryl-(lower alkyl)" means the "lower alkyl" group substituted by "aryl" and include benzyl,

naphthylmethyl, 1-phenethyl, 2-phenethyl, 1-naphthylmethyl, 2-naphthylmethyl, 3-phenylpropyl, 3-naphthylpropyl, 4-phenylbutyl, 4-naphthylbutyl, 6-phenylhexyl, 6-naphthylhexyl and the like, and it is preferably phenyl-(lower alkyl), more preferably phenyl-(C1-C4 alkyl), more preferably phenyl-(C1-C2 alkyl), most preferably benzyl. And the "aryl-(lower alkyl)" may have 1 to 3 substituent(s) on the aryl group, the number of substituent is preferably 1 or 2, more preferably 1, in case that "aryl-(lower alkyl)" has plural substituents, they may be the same or different each other, but, needless to say, "aryl-(lower alkyl)" may not have substituent.

The "heteroaryl-(lower alkyl)" means the "lower alkyl" group substituted by "heteroaryl" such as pyrrolylmethyl, thienylmethyl, furylmethyl, pyridylmethyl, oxazolylmethyl, thiazolylmethyl, pyrrolylethyl, pyridylethyl, oxazolylethyl, thiazolylethyl, pyridylbutyl, oxazolylbutyl, thiazolylbutyl or the like, and it is preferably (6-membered heteroaryl)-(C1-C4 alkyl), more preferably (6-membered heteroaryl)-(C1-C2 alkyl), most preferably pyridylmethyl. And the "heteroaryl-(lower alkyl)" may have 1 to 3 substituent(s) on the heteroaryl group, the number of substituent is preferably 1 or 2, more preferably 1, in case that "heteroaryl-(lower alkyl)" has plural substituents, they may be the same or different each other, but, needless to say, "heteroaryl-(lower alkyl)" may not have substituent.

The "cycloalkyl" means C3-C10 cycloalkyl group, such

as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, norbornyl, adamantyl, and the like, and it is preferably cyclohexyl or adamantyl. So, the partial structure:  is exemplified

 and the like.

The "lower alkoxy" means a straight or branched chain aliphatic hydrocarbon oxy group, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, tert-butoxy, pentoxy, hexoxy, and the like, and it is preferably C1-C4 alkoxy, more preferably C1-C2 alkoxy, most preferably methoxy.

The "halogen" may include a fluorine atom, a chlorine atom, a bromine or a iodine atom, more preferably a chlorine atom.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. This invention includes both mixtures and separate individual isomers. However, in the portion of 2-cyanopyrrolidine, (2S) isomer is more preferable, and in the portion of 2-cyanooxazolidine and 2-cyanothiazolidine, (4R) isomer is more preferable.

Oxime derivatives may have two kind of geometrical isomers, that is, (syn) form and (anti) form, this invention includes both isomers.

The compounds of the formula (I) may also exist in

tautomeric forms and this invention includes both mixtures and separate individual tautomers.

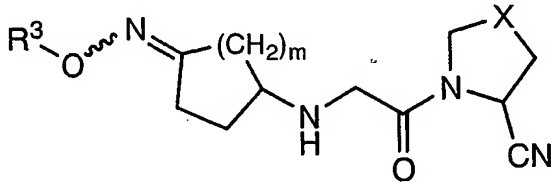
The compounds of the formula (I) and its salts may be in a form of a solvate such as hydrate, which is included within the scope of the present invention.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

The compounds of this invention may be converted to salt according to a conventional method. Suitable salts of the compounds (I) are pharmaceutically acceptable conventional non-toxic salts such as an organic acid salt (e.g., acetate, maleate, tartrate, methanesulfonate, benzenesulfonate, formate, toluenesulfonate, trifluoroacetate, etc.), an inorganic acid salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.), or the like, and the preferable salt is hydrochloride or trifluoroacetate salt.

The Compound (I) may preferably include;

a compound of the formula (II)



(II)

[wherein

X is CH_2, O or S,

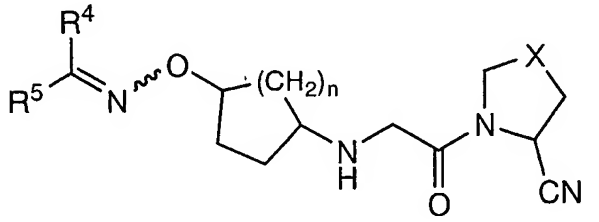
R^3 is lower alkyl, aryl (which may have 1 to 3 substituent(s) selected from the group described later),

heteroaryl (which may have 1 to 3 substituent(s) selected from the group described later), aryl-(lower alkyl) (which may have 1 to 3 substituent(s) selected from the group described later on the aryl group), or heteroaryl-(lower alkyl) (which may have 1 to 3 substituent(s) selected from the group described later on the heteroaryl group),

m is integer of 1 to 3

the substituent(s) is selected from the group consisting of lower alkyl, halogen, cyano, nitro, amino and hydroxy],

a compound of the formula (III)



(III)

[wherein

X is CH_2, O or S,

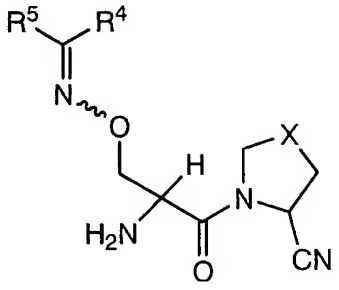
R^4 is hydrogen or lower alkyl,

R^5 is lower alkyl, aryl (which may have 1 to 3 substituent(s) selected from the group described later), or heteroaryl (which may have 1 to 3 substituent(s) selected from the group described later),

n is integer of 1 to 3

the substituent(s) is(are) selected from the group consisting of lower alkyl, halogen, cyano, nitro, amino and hydroxy],

a compound of the formula (IV)



(IV)

[wherein

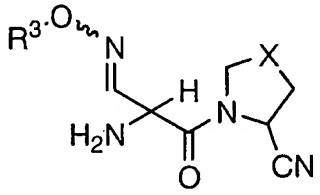
X is CH_2, O or S,

R^4 is hydrogen or lower alkyl,

R^5 is lower alkyl, aryl (which may have 1 to 3 substituent(s) selected from the group described later), or heteroaryl (which may have 1 to 3 substituent(s) selected from the group described later),

the substituent(s) is(are) selected from the group consisting of lower alkyl, halogen, cyano, nitro, amino and hydroxy] , and

a compound of the formula (V)



(V)

[wherein

X is CH_2, O or S,

R^3 is lower alkyl, aryl (which may have 1 to 3 substituent(s) selected from the group described later), heteroaryl (which may have 1 to 3 substituent(s) selected from the group described later), aryl-(lower alkyl) (which may have 1 to 3 substituent(s) selected from the group

described later on the aryl group), or heteroaryl-(lower alkyl) (which may have 1 to 3 substituent(s) selected from the group described later on the heteroaryl group),

the substituent(s) is(are) selected from the group consisting of lower alkyl, halogen, cyano, nitro, amino and hydroxy].

And in the each definition of the compound formula(I), preferably,

(1) X is CH_2 or S,

(2) X is CH_2,

(3) R^3 is lower alkyl, aryl-(lower alkyl) (which may have 1 to 3 substituent(s) on the aryl group), or heteroaryl-(lower alkyl) (which may have 1 to 3 substituent(s) on the heteroaryl group),

(4) R^3 is C1-C4 alkyl, aryl-methyl (which may have 1 to 3 substituent(s) on the aryl group), or heteroaryl-methyl (which may have 1 to 3 substituent(s) on the heteroaryl group),

(5) R^3 is C1-C4 alkyl, benzyl (which may have 1 to 3 substituent(s) on the phenyl group), or pyridylmethyl (which may have 1 to 3 substituent(s) on the pyridyl group),

(6) m is 2,

(7) R^4 is hydrogen,

(8) R^4 is C1-C2 alkyl,

(9) R^5 is C1-C2 alkyl, phenyl (which may have 1 to 3 substituent(s)), pyridyl (which may have 1 to 3 substituent(s))

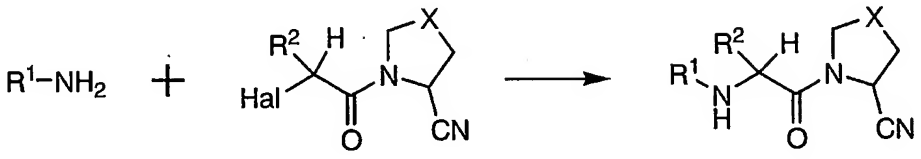
(10) R^5 is pyridyl (which may have 1 to 3 substituent(s)),

(11) n is 2,

(12) substituent(s) is(are) cyano.

The compound of the formula (I) of the present invention can be prepared according to the following process A-1 to A-3.

[Process A-1]



(VI) (VII) (I)

In the above formulae, R^1, R^2 and X represent the same meanings as defined above. And "Hal" represents halogen atom, especially, chlorine or bromine atom.

Process A-1 is the process for preparing the Compound (I) from amine Compound (VI) and halogen Compound (VII) in solvent, preferably in the presence of base.

Compound (VI) and (VII) may be purchased if it is commercial, or synthesized according to Processes C and B, respectively, mentioned after or other general methods obvious to the person skilled in the organic chemistry from commercial compounds.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include ethers such as diisopropyl ether, tetrahydrofuran, dioxane, preferably tetrahydrofuran.

The base employable in this process for making basic condition is not particularly limited so long as it accelerates this reaction and may include organic amines

such as triethylamine, tributylamine, diisopropylethylamine; alkali metal hydrogencarbonates such as litium hydrogencarbonate, sodium hydrogencarbonate and potassium hydrogencarbonate; alkali metal carbonates such as lithium carbonate, sodium carbonate and potassium carbonate; alkaline earth metal carbonates such as magnesium carbonate and calcium carbonate; alkali metal hydroxides such as lithium hydroxide, sodium hydroxide and potassium hydroxide, preferably organic amine, especially triethylamine.

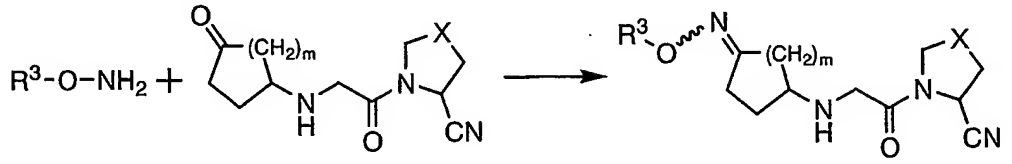
This process is generally carried out by adding the solution of Compound (VII) preferably dropwise to the solution of Compound (VI). The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually from -10℃ to 20℃. And after adding, the temperature is preferably raised to room temperature.

The reaction time after the adding varies depending on the starting material, the solvent, etc., but it is usually from 1hr to 24hrs, preferably from 1hr to 15hrs.

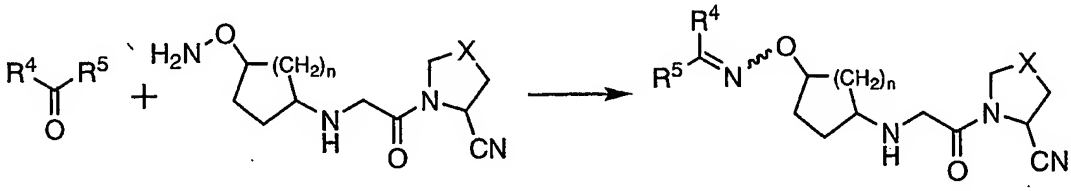
After the reaction, the mixture is quenched by aqueous solvent such as water, saturated NH_4Cl, hydrochloric acid, etc, and extracted with organic solvent insoluble with water such as ethyl acetate, $CHCl_3$, etc. If the target compound is in aqueous layer, base such as $NaHCO_3$ is added. Preferably, the organic layer is washed with water or the like, dried over anhydrous $MgSO_4$ or Na_2SO_4, evaporated in vacuo, and the target compound is purified by the conventional method such as thin layer chromatography, silica gel column chromatography, etc.

Compound (II) and (III) included in the scope of Compound (I) can be synthesized by following Process A-2.

[Process A-2]



(VIII) (IX) (II)



(X) (XI) (III)

In the above formulae, R^3 to R^5, X, m and n represent the same meanings as defined above.

Process A-2 is the process for preparing the Compound (II) and (III) by forming oxyimino group from aminooxy compound and carbonyl compound in solvent. And Compound (II) and (III) are the Compound (I), of which the definition R^1 is not hydrogen or lower alkyl.

Starting Compound (VIII) to (XI) may be purchased if they are commercial, or synthesized according to general methods from commercial compounds. For example, aminooxy group of Compound (VIII) and (XI) can be synthesized by application of Process D described later.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include alcohols such as methanol,

ethanol, isopropanol, preferably methanol. But, in case that Compound (X) may be used as solvent, other solvent is not necessarily needed.

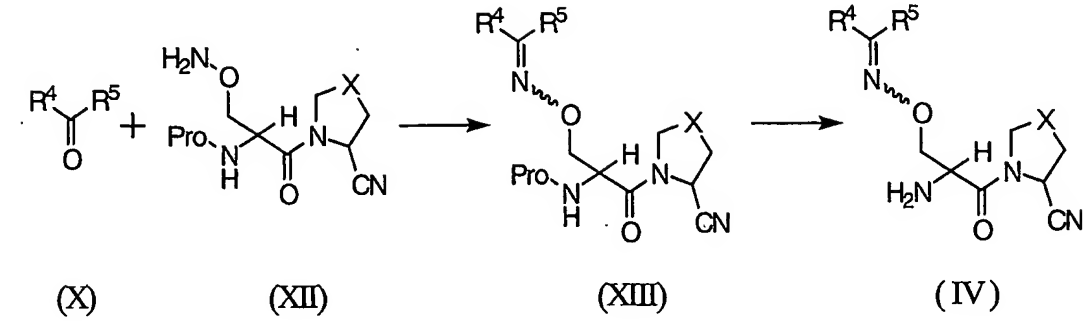
This process is generally carried out by adding the solution of carbonyl compound (Compound (IX) or (X)) to the solution of aminooxy compound (Compound (VIII) or (XI)). The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually from 10℃ to 50℃, preferably room temperature.

The reaction time after the adding varies depending on the starting material, the solvent, etc., but it is usually from 30min to 12hrs, preferably from 1hr to 5hrs.

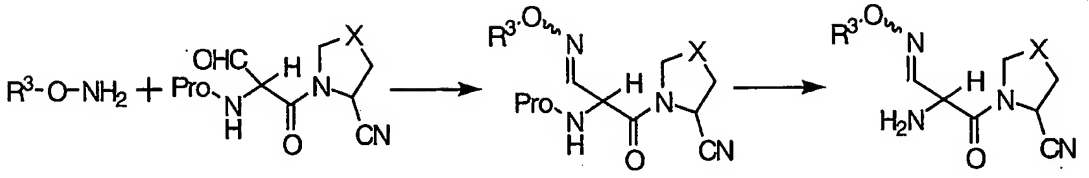
After the reaction, the solvent is removed in vacuo, and the residue is dissolved in organic solvent insoluble with water such as ethyl acetate, $CHCl_3$, etc. The solution is washed with aqueous solvent such as brine, and dried over anhydrous $MgSO_4$ or Na_2SO_4, evaporated in vacuo. The target compound may be purified by the conventional method such as silica gel column chromatography, etc.

Compound (IV) and (V) included in the scope of Compound (I) can be synthesized by following Process A-3.

[Process A-3]



(X) (XII) (XIII) (IV)



(VIII) (XIV) (XV) (V)

In the above formulae, R^3 to R^5 and X represent the same meanings as defined above. And "Pro" means the protective group of amino group.

Process A-3 is the process for preparing the Compound (IV) and (V) by forming oxyimino group from aminooxy compound and carbonyl compound in solvent similar to Process A-2, then deprotecting step. And Compound (IV) and (V) are the Compound (I), of which the definition R^2 is not hydrogen.

In the first step (forming oxyimino group), the same procedure as that in Process A-2 may be adopted in this process, because forming of oxyimino group is common to both of Process.

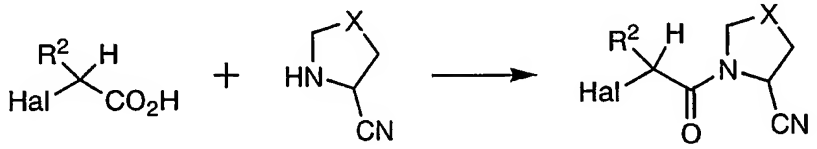
In the second step (deprotecting), concerning the kind of protective group ("Pro") and cleavage reaction of the protective group, 「PROTECTIVE GROUPS IN ORGANIC SYNTHESIS Second Edition」 T.W.Green and P.G.M.Wuts, John

Wiley & Sons, INC. may be referred.

For example, when "Pro" group is carbamate group such as tert-butoxycarbonyl group, the cleavage reaction is carried out in the acidic condition in solvent by acid such as hydrochloric acid, trifluoroacetic acid, or the like. After the deprotection, excess acid and solvent are removed in vacuo, and the target compound may be purified by triturating, which uses appropriate solvent such as diethylether.

Compound (VII), which is the starting compound of Process A-1, can be synthesized by following Process B.

[Process B]



(XVI) (XVII) (VII)

In the above formulae, R^2, X and "Hal" represent the same meanings as defined above.

Process B is the process for preparing the Compound (VII) by forming amide bond in solvent in the presence of dehydrating agent, base and catalyst.

Compound (XVI) and (XVII) may be purchased if it is commercial, or synthesized according to general methods obvious to the person skilled in the organic chemistry from commercial compounds.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include amides such as dimethylformamide and dimethylacetamide.

The dehydrating agent employable in this process is not particularly limited so long as it accelerate forming amide bond and may include carbodiimide compounds such as dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide, water solvable carbodiimide (WSCD), preferably WSCD.

The base employable in this process is not particularly limited so long as it accelerates this process and may include organic amines such as triethylamine, tributylamine, diisopropylethylamine (DIEA), preferably DIEA.

The catalyst employable in this process is not particularly limited so long as it can mainly make the carboxyl group of Compound (XVI) active and may include 1-hydroxybenzotriazole (HOBT).

This process is generally carried out by adding the dehydrating agent and base to the solution of Compound (XVI), Compound (XVII) and catalyst. The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually from -10℃ to 30℃, preferably from 0℃ to 10℃. And after adding, the temperature is preferably raised to room temperature.

The reaction time after the adding varies depending on the starting material, the solvent, etc., but it is usually from 2hrs to 24hrs.

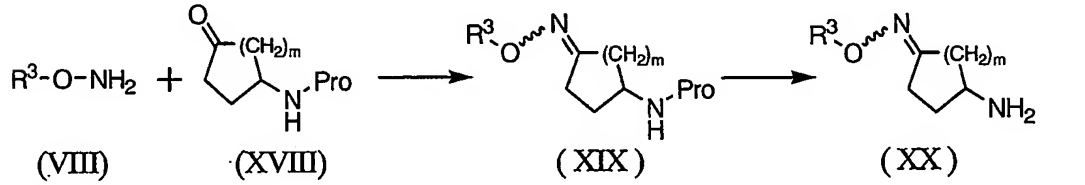
After the reaction, the solvent is removed in vacuo, the target compound may be purified by the conventional method such as silica gel column chromatography, etc.

Compound (XX) and (XXIII), both of which are the

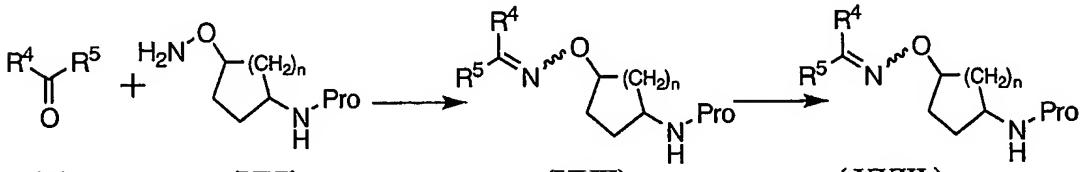
starting Compound (VI) of Process A-1, can be synthesized by following Process C. Provided that Compound (XX) and (XXIII) are the Compound (VI), of which the R^1 is not hydrogen or lower alkyl.

Incidentally, in case that R^1 of Compound (VI) is hydrogen or lower alkyl, its structure is very simple. So, the compound may be purchasable.

[Process C]



(VIII) (XVIII) (XIX) (XX)



(X) (XXI) (XXII) (XXIII)

In the above formulae, R^3 to R^5, m, n and "Pro" represent the same meanings as defined above.

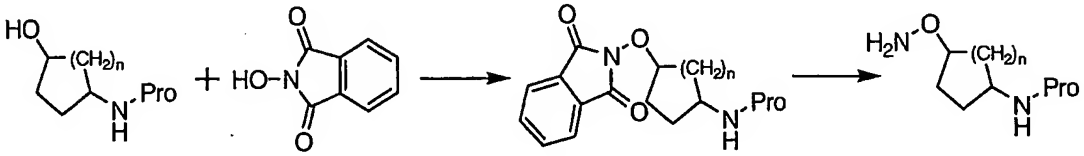
Process C is the process for preparing the Compound (XX) and (XXIII) by forming oxyimino group from amino compound and carbonyl compound in solvent.

And the same procedure as that in Process A-2 may be adopted in this process, because forming of oxyimino group is common to both of Process.

The compound having aminooxy group such as Compound (VIII) and (XI) (the starting compound of Process A-2, and the like), Compound (XII) (the starting compound of Process A-3), Compound (XXI) (the starting compound of

Process C), can be synthesized by following Process D. But, in the following reaction formula, the synthesis process of Compound (XXI) is shown as representative example.

[Process D]



(XXIV) (XXV) (XXVI) (XXI)

In the above formulae, n and "Pro" represent the same meanings as defined above.

Process D is the process for preparing the compound having aminooxy group by functional group trans formation from hydroxy group.

In this process, first, to the solution of the compound having hydroxy group (Compound (XXIV)), Compound (XXV) and triphenylphosphine was added diisopropyl azodicarboxylate (DIAD).

The compound having hydroxy group may be purchased if it is commercial, or synthesized according to general methods obvious to the person skilled in the organic chemistry from commercial compounds. And Compound (XXV) may be purchasable.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include ethers such as diisopropyl ether, tetrahydrofuran, dioxane, preferably tetrahydrofuran.

The temperature when adding the dehydrating agent (DIAD) varies depending on the starting material, the solvent, etc., but it is usually from -10℃ to 50℃,

preferably from 0℃ to 30℃.

The reaction time after the adding varies depending on the starting material, the solvent, etc., but it is usually from 30min to 12hrs.

After the reaction, to the solution water, then extracted with organic solvent insoluble with water such as ethyl acetate, $CHCl_3$, etc. The organic layer is dried over anhydrous $MgSO_4$ or Na_2SO_4, evaporated in vacuo. And by adding the solvent to dissolve the target compound but not to able dissolve triphenylphosphonate, the target compound (phthalimide derivative) may be obtained. The phthalimide derivative may be used in next step without further purification.

Then, phthalimide derivative (Compound (XXVI)) was decomposed by hydrazine in solvent. That is, to the solution of phthalimide derivative, hydrazine is added.

The solvent employable in this process is not particularly limited so long as it is inactive in this reaction and may include alcohols such as methanol, ethanol, isopropanol, preferably ethanol.

The temperature at that time varies depending on the starting material, the solvent, etc., but it is usually from 50℃ to 150℃, preferably from 70℃ to 130℃.

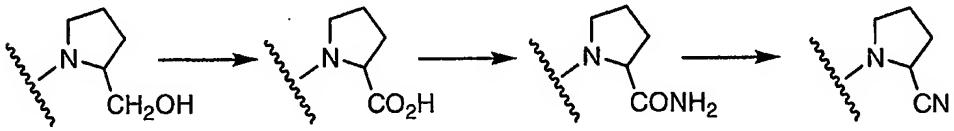
The reaction time after the adding varies depending on the starting material, the solvent, etc., but it is usually from 5min to 5hrs.

After the reaction, the resulting precipitate is filtered off and washed with solvent, and filtrate is concentrated. Then, to the residue, aqueous solvent and organic solvent insoluble with water such as ethyl acetate

are added, aqueous layer is basified and extracted. The organic layer is dried over anhydrous $MgSO_4$ or Na_2SO_4, evaporated in vacuo to obtain the target compound. If necessary, further purification may be carried out.

In the above processes, functional group trans formation may be carried out on cue so long as the other sites of the compounds are not affected. In the following reaction formula, the functional group trans formation of the pyrrolidine ring is shown as representative example.

[Process E]



Process E shows the representative example of functional group trans formation. Accordingly, other reactions of functional group trans formation may be carried out.

Above processes, all starting materials and product compounds may be salts. The compounds of above processes can be converted to salt according to a conventional method. For example of making hydrochloride or trifluoroacetate, to the compound, the solution of hydrochloride such as 4N hydrochloride/dioxane or trifluoroacetic acid is added, then the solvent and excess acid is removed and the reside is triturated appropriate solvent such as diethylether.

For therapeutic purpose, the Compound (I) and a

pharmaceutically acceptable salt thereof of the present invention can be used in a form of pharmaceutical preparation containing one of said compounds as an active ingredient, in admixture with a pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient suitable for oral, parenteral or external administration. The pharmaceutical preparations may be capsules, tablets, dragees, granules, inhalant, suppositories, solution, lotion, suspension, emulsion, ointment, gel, cream, or the like. If desired, there may be included in these preparations, auxiliary substances, stabilizing agents, wetting or emulsifying agents, buffers and other commonly used additives.

While the dosage of therapeutically effective amount of the Compound (I) will vary depending upon the age and condition of each individual patient, an average single dose of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg and 1000 mg of the Compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000 mg/body may be administered per day.

Best Mode for Carrying Out the Invention

The patents, patent applications and publications cited herein are incorporated by reference.

The following Examples are given only for the purpose of illustrating the present invention in more detail.

Abbreviations used in this application are as follows,
TLC : thin layer chromatography.

Example 1-1

tert-Butyl (1S)-2-[(2S)-2-carbamoyl-1-pyrrolidinyl]-2-oxo-1-[[[(3-pyridinylmethylidene)amino]oxy]methyl]ethylcarbamate

To a solution of tert-butyl (1S)-1-[(aminooxy)methyl]-2-[(2S)-2-carbamoyl-1-pyrrolidinyl]-2-oxoethylcarbamate (120mg) in methanol (5ml) was added nicotinaldehyde (0.036ml) at room temperature. The reaction mixture was set aside at room temperature for 2hrs.

After removal of the solvent in vacuo, the residue was dissolved in ethyl acetate (10ml), washed with brine(5ml), and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified with silica gel TLC (0.5mm X 2, $CHCl_3$:methanol=20:1) to give the target compound as a colorless oily amorphous (120mg, 78%).

^{1}H NMR($CDCl_3$) : 1.45(s, 9H), 1.90-2.40(m, 4H), 3.60-3.77(m, 2H), 4.34-4.40(m, 2H), 4.64-4.69(m, 1H), 4.85-4.94(m 1H),

5.21-5.28(m, 1H), 5.37-5.44(m, 1H), 6.68(br-s, 1H), 7.28-7.36(m, 1H), 7.90-7.95(m, 1H), 8.10(s, 1H), 8.62-8.65(m, 1H), 8.74(s, 1H)

MS : 406.17 (ES+)

Example 1-2

tert-Butyl (1S)-2-[(2S)-2-cyano-1-pyrrolidinyl]-2-oxo-1-[[[(3-pyridinylmethylidene)amino]oxy]methyl]ethylcarbamate

To a slurry of tert-butyl (1S)-2-[(2S)-2-carbamoyl-1-pyrrolidinyl]-2-oxo-1-[[[(3-pyridinylmethylidene)amino]oxy]methyl]ethylcarbamate(120mg) obtained by Example 1-1 in tetrahydrofuran (3ml) were added triethylamine (0.1ml) and trifluoroacetic anhydride (0.084ml) dropwise at 5℃ (clearly solved). The reaction mixture was stirred at 5℃ for 30min.

Sat.$NaHCO_3$ was added and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was purified with TLC (0.5mm X 1, $CHCl_3$:methanol=20:1) to give the target compound as a colorless oily amorphous (75mg, 65.4%).

^{1}H NMR($CDCl_3$) : 1.43(s, 9H), 2.06-2.31(m, 4H), 3.65-3.81(m, 2H), 4.35-4.40(m, 2H), 4.76-4.85(m, 2H), 5.32-5.40(m, 1H), 7.28-7.36(m, 1H), 7.94-8.00(m, 1H), 8.13(s, 1H), 8.60-8.65(m, 1H), 8.74(s, 1H)

MS : 388.14 (ES+)

Example 1-3

(2S)-1-[(2S)-2-Amino-3-[[(3-pyridinylmethylidene)amino]oxy]propanoyl]-2-cyanopyrrolidine trifluoroacetate

tert-Butyl (1S)-2-[(2S)-2-cyano-1-pyrrolidinyl]-2-oxo-1-[[[(3-pyridinylmethylidene)amino]oxy]methyl]ethylcarbamate (70mg) obtained by Example 1-2 dissolved in trifluoroacetic acid (2ml) at room temperature, and the reaction mixture was stirred at room temperature for 30min.

After removal of the solvent in vacuo, the residue was triturated with diethylether to give the target compound as a pale yellow solid (45mg, 62.1%).

^{1}H NMR(DMSO-d_6) : 1.95-2.33(m, 4H), 3.64-3.79(m, 2H), 4.44-4.64(m, 3H), 4.77-4.87(m, 1H), 7.50-7.58(m,1H), 8.14-8.21(m, 1H), 8.40(s, 1H), 8.41-8.89(m, 4H)
MS : 288.12(ES+), free 287.32

Example 2-1
cis-tert-Butyl 4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]cyclohexylcarbamate

To a solution of trans-tert-butyl 4-hydroxycyclohexylcarbamate (3g), 2-hydroxy-1H-isoindole-1,3(2H)-dione (2.27g), and triphenylphosphine (3.84g) in tetrahydrofuran (30ml) was added diisopropyl azodicarboxylate (DIAD, 3.02ml) dropwise at 5℃. The reaction mixture was stirred at room temperature for 2hrs.

Then, water (10ml) was added and extracted with ethyl

acetate (50ml). The organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo, the residue was triturated with isopropylether, the resulting precipitate (triphenylphosphonate) was filtered off. The filtrate was concentrated to give the yellow oil (5.0g, 99.6%). Further purification was not attempted.

Example 2-2

cis-tert-Butyl 4-(aminooxy)cyclohexylcarbamate

To a solution of the crude cis-tert-butyl 4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]cyclohexylcarbamate (5g) obtained by Example 2-1 in ethanol (50ml) was added hydrazine hydrate (7ml) at 120℃ (bath temp.). After 10min, the reaction mixture gave white precipitate (phthalhydrazine).

The resulting precipitate was filtered off, and the filtrate was concentrated. The residue was dissolved in 1N HCl (40ml) and ethyl acetate (40ml). The aqueous layer was basified with $NaHCO_3$, and saturated with NaCl, and extracted with ethyl acetate (40ml). The organic layer was dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was crystallized from isopropylether and collected by filtration to give the target compound as a white powder (1.16g, 36.3%).

^{1}H NMR($CDCl_3$) : 1.44(s, 9H), 1.45-1.91(m, 8H), 3.50(br-s, 1H), 3.64(br-s, 1H), 4.48(br-s, 1H), 5.23(s, 2H)

MS : 231.17 (ES+)

Example 2-3

cis-tert-Butyl 4-[[(3-pyridinylmethylidene)amino]-oxy]cyclohexylcarbamate

To a solution of cis-tert-butyl 4-(aminooxy)cyclohexylcarbamate (200mg) obtained by Example 2-2 in methanol (4ml) was added nicotinaldehyde (93mg) at room temperature. The reaction mixture was set aside at room temperature for 2hrs.

After removal of the solvent in vacuo, the residue was dissolved in ethyl acetate, washed with brine, and dried over $MgSO_4$. After removal of the solvent in vacuo, the target compound was obtained as a colorless oily amorphous (200mg, 72.1%). Further purification was not attempted.

^1H NMR($CDCl_3$) : 1.45(s, 9H), 1.46-2.06(m, 8H), 3.55(br-s, 1H), 4.33(br-s, 1H), 4.50(br-s, 1H), 7.28-7.32(m, 1H), 7.95-7.98(m, 1H), 8.10(s, 1H), 8.57-8.60(m, 1H), 8.73(s, 1H)

MS : 320.18(ES+)

Example 2-4

cis-Nicotinaldehyde O-(4-aminocyclohexyl)oxime

cis-tert-Butyl 4-[[(3-pyridinylmethylidene)-amino]oxy]cyclohexylcarbamate (200mg) obtained by Example 2-3 was dissolved in small amount of methanol, and 4N HCl-dioxane (5ml) was added at room temperature.

After 30min, the solvent was removed in vacuo, the

residue was basified with sat.$NaHCO_3$ and extracted with $CHCl_3$ (5 times). The organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo, the target compound was obtained as colorless oil (120mg, 87.4%).

^1H NMR($CDCl_3$) : 1.46-2.15(m, 8H), 2.16-2.37(br-s, 2H), 2.80-2.90(m, 1H), 4.34-4.40(m, 1H), 7.30-7.32(m, 1H), 7.93-7.97(m, 1H), 8.12(s, 1H), 8.57-8.60(m, 1H), 8.74(s, 1H)

MS : 220.14 (ES+)

Example 2-5

cis-(2S)-1-[[[4-[[(3-Pyridinylmethylidene)amino]oxy]cyclohexyl]amino]acetyl]-2-cyanopyrrolidine dihydrochloride

To a solution of cis-nicotinaldehyde O-(4-aminocyclohexyl)oxime (120mg) obtained by Example 2-4 and triethylamine (0.077ml) in tetrahydrofuran (4ml) was added a solution of (2S)-1-bromoacetyl-2-cyanopyrrolidine (60mg) in tetrahydrofuran (1ml) dropwise at 5℃.

After 2hrs, the reaction mixture was diluted with sat.NH_4Cl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo, the residue was purified with TLC (0.5mm X 1, CHCl3:methanol=10:1).

After removal of the solvent in vacuo, the oily amorphous was dissolved in methanol and 4N HCl-dioxane.

After removal of the solvent, the residue was triturated with diethylether and the solvent was removed in vacuo. The target compound was obtained as a white powder (50mg, 42.2%).

^{1}H NMR(DMSO-d_6) : 1.60-2.22(m, 12H), 3.13(br-s, 1H), 3.45-3.74(m, 2H), 3.90-4.15(m, 2H), 4.41(br-s, 1H), 4.85(m, 1H), 7.89-7.95(m, 1H), 8.47(s, 1H), 8.57-8.60(m,1H), 8.86(m, 1H), 9.06(s, 1H), 9.20(br-s, 1H)
MS : 356.13(ES+), free 355.43

Example 3-1
cis-tert-Butyl 4-[[(1-methylethylidene)amino]oxy]-cyclohexylcarbamate

To a solution of cis-tert-butyl 4-(aminooxy)cyclohexylcarbamate (400mg) in methanol (2ml) was added acetone (10ml) at room temperature. The reaction mixture was set aside at room temperature for 2hrs.

After removal of the solvent in vacuo, the residue was dissolved in ethyl acetate, washed with brine, and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was crystallized from n-hexane to give the target compound as a white solid (460mg, 98%).

^{1}H NMR($CDCl_3$) : 1.40-1.95(m, 8H), 1.44(s, 9H), 1.86(s, 3H), 1.87(s, 3H), 3.60-3.67(m, 1H), 4.13-4.19(m, 1H)
MS : 271.21(ES+)

Example 3-2

Acetone O-(4-aminocyclohexyl)oxime

tert-Butyl 4-[[(1-methylethylidene)amino]oxy]-cyclohexylcarbamate (460mg) obtained by Example 3-1 was dissolved in small amount of methanol, and 4N HCl-dioxane (5ml) was added at room temperature.

After 30min, the solvent was removed in vacuo, the residue was basified with sat. $NaHCO_3$ and extracted with $CHCl_3$ (5 times). The organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo, the residual solid was triturated with isopropylether and collected by filtration to give the target compound as a white powder (200mg, 69%).

^1H NMR($CDCl_3$) : 1.45-2.14(m, 8H), 1.87(s, 3H), 1.91(s, 3H), 3.15-3.25(m, 1H), 4.20-4.25(m, 1H)

MS : 171.04(ES+)

Example 3-3

cis-(2S)-1-[[[4-[[(1-Methylethylidene)amino]oxy]cyclohexyl]amino]acetyl]-2-cyanopyrrolidine hydrochloride

To a solution of cis-acetone O-(4-aminocyclohexyl)oxime (200mg) obtained by Example 3-2 and triethylamine (0.17ml) in tetrahydrofuran (4ml) was added a solution of (2S)-1-bromoacetyl-2-cyanopyrrolidine (130mg) in tetrahydrofuran (1ml) dropwise at 5℃.

After 12hrs, the solvent was removed in vacuo, the

residue was treated with diethylether and 1N HCl. The aqueous layer was separated, basified with $NaHCO_3$, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo, the residue was purified with TLC (0.5mm X 1, $CHCl_3$:methanol=20:1). The residue was dissolved in small amount of methanol and 4N HCl-dioxane was added. After removal of the solvent in vacuo, the target compound was obtained as a white solid (25mg, 12.2%).

^1H NMR(DMSO-d_6) : 1.40-2.23(m, 12H), 1.82(s, 3H), 1.86(s, 3H), 3.38-4.90(m, 7H)

MS : 307.20(ES+), free 306.40

Example 4-1

cis-tert-Butyl 4-[[(2-pyridinylmethylidene)amino]-oxy]cyclohexylcarbamate

To a solution of cis-tert-butyl 4-(aminooxy)cyclohexylcarbamate (200mg) in methanol (4ml) was added 2-pyridinecarbaldehyde (0.083ml) at room temperature. The reaction mixture was set aside at room temperature for 2hrs.

After removal of the solvent in vacuo, the target compound was obtained as a yellow oil (260mg, 93.7%). Further purification was not attempted.

Example 4-2

cis-2-Pyridinecarbaldehyde O-(4-aminocyclohexyl)oxime

cis-tert-Butyl 4-[[(2-pyridinylmethylidene)-amino]oxy]cyclohexylcarbamate (260mg) obtained by Example 4-1 was dissolved in small amount of methanol, and 4N HCl-dioxane (5ml) was added at room temperature.

After 30min, the solvent was removed in vacuo, the residue was basified with sat.$NaHCO_3$ and extracted with $CHCl_3$ (5 times). The organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo, the target compound was obtained as colorless oil (180mg, about 100%).

^1H NMR($CDCl_3$) : 1.55-2.27(m, 8H), 3.16-3.27(m, 1H), 3.71(s, 2H), 4.40-4.45(m, 1H), 7.23-7.30(m, 1H), 7.64-7.75(m, 2H), 8.22(s, 1H), 8.61-8.62(m, 1H)

MS : 220.18(ES+)

Example 4-3

cis-(2S)-1-[[[4-[[(2-Pyridinylmethylidene)amino]oxy]cyclohexyl]amino]acetyl]-2-cyanopyrrolidine dihydrochloride

To a solution of cis-2-pyridinecarbaldehyde O-(4-aminocyclohexyl)oxime (180mg) obtained by Example 4-2 and triethylamine(0.116ml) in tetrahydrofuran (2ml) was added a solution of (2S)-1-bromoacetyl-2-cyanopyrrolidine (90mg) in tetrahydrofuran (1ml) dropwise at 5℃.

After 2hrs stirring at room temperature, the reaction mixture was diluted with sat.NH_4Cl and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and

filtered. After removal of the solvent in vacuo, the residue was purified with TLC (0.5mm, $CHCl_3$:methanol=10:1). After removal of the solvent in vacuo, the residual oily amorphous was dissolved in methanol and 4N HCl-dioxane. After removal of the solvent, the residue was triturated with diethylether and the solvent was removed in vacuo, the target compound was obtained as a white powder (50mg, 28.2%).

^{1}H NMR(DMSO-d_6) : 1.56-2.25(m, 12H), 3.17(br-s, 1H), 3.44-3.70(m, 2H), 3.97-4.40(m, 3H), 4.80-4.86(m, 1H), 7.60-7.75(m, 1H), 7.93-7.98(m, 1H), 8.05-8.13(m, 1H), 8.36(s, 1H), 8.68-8.70(m, 1H), 9.13(br-s, 1H)
MS : 356.24(ES+), free 355.43

Example 5-1
tert-Butyl (1S)-2-[(2S)-2-carbamoyl-1-pyrrolidinyl]-1-hydroxymethyl-2-oxoethylcarbamate

To a solution of (2S)-2-[(tert-butoxycarbonyl)amino]-3-hydroxypropanoic acid (5g), (2S)-2-pyrrolidinecarboxamide (2.78g), and 1-hydroxybenzotriazole hydrate (HOBT-H_2O, 4.47g) in N,N-dimethylformamide (DMF, 50ml) were added 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (WSCD-HCl, 5.14g) and diisopropylethylamine (DIEA, 5.1ml) at 5℃. The reaction mixture was stirred at room temperature overnight.

The solvent was removed in vacuo, and the resulting residue was purified with silica gel column chromatography

(SiO_2 200ml, $CHCl_3$:methanol=10:1). After removal of the solvent in vacuo, the residual oil was triturated with diethylether and solidified, washed with diethylether to give the target compound as a white powder (5g, 68.1%).

^1H NMR($CDCl_3$) : 1.43(s, 9H), 1.90-2.22(m, 4H), 3.56-3.96(m, 4H), 4.25-4.70(m, 3H), 5.75(m, 1H), 6.31(s, 1H), 6.94(s, 1H)

MS : 302.16 (ES+)

Example 5-2

tert-Butyl (1S)-2-[(2S)-2-carbamoyl-1-pyrrolidinyl]-1-[[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]methyl]-2-oxoethylcarbamate

To a solution of tert-butyl (1S)-2-[(2S)-2-carbamoyl-1-pyrrolidinyl]-1-hydroxymethyl-2-oxoethylcarbamate (2g) obtained by Example 5-1, 2-hydroxy-1H-isoindole-1,3(2H)-dione (1.08g) and triphenylphosphine (1.8g) in tetrahydrofuran (20ml) was added diisopropyl azodicarboxylate (DIAD, 1.44ml) dropwise at 5℃. The reaction mixture was stirred at 5℃ for 1hr.

The resulting gel was collected by filtration, washed with tetrahydrofuran. The collected solid was used for the next step without further purification (3g, about 100%).

Example 5-3

tert-Butyl (1S)-2-[(2S)-2-carbamoyl-1-pyrrolidinyl]-

1-[(aminooxy)methyl]-2-oxoethylcarbamate

To a solution of tert-butyl (1S)-2-[(2S)-2-carbamoyl-1-pyrrolidinyl]-1-[[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]methyl]-2-oxoethylcarbamate (900mg) obtained by Example 5-2 in ethanol (10ml) was added hydrazine hydrate (1ml) at 120℃ (bath temp.). After 10min, the reaction mixture gave white precipitate (phthalhydrazine).

The resulting precipitate was filtered off, and the filtrate was concentrated. The residue was dissolved in 1N HCl and ethyl acetate. The aqueous layer was separated, basified with $NaHCO_3$ carefully, saturated with NaCl, and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo, the target compound was obtained as a colorless oily amorphous (800mg, 37.6%).

^{1}H NMR($CDCl_3$) : 1.45(s, 9H), 1.62-1.71(m, 2H), 2.00-2.07(m, 2H), 2.32-2.37(m, 1H), 3.67-3.91(m, 4H), 4.63-4.78(m, 2H), 5.36-5.70(m, 4H)

MS : 317.20(ES+)

Example 5-4

tert-Butyl (1S)-2-[(2S)-2-carbamoyl-1-pyrrolidinyl]-2-oxo-1-[[[(2-pyridinylmethylidene)amino]oxy]methyl]ethylcarbamate

To a solution of tert-butyl (1S)-2-[(2S)-2-carbamoyl-1-pyrrolidinyl]-1-[(aminooxy

)methyl]-2-oxoethylcarbamate (200mg) obtained by Example 5-3 in methanol (4ml) was added 2-pyridinecarbaldehyde (0.06ml) at room temperature. The reaction mixture was set aside at room temperature for 2hrs.

After TLC check, the solvent was removed in vacuo, the residue was dissolved in ethyl acetate, washed with brine, and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was purified with TLC (0.5mm X 2, $CHCl_3$:methanol=20:1) to give the target compound as a colorless oily amorphous (120mg, 46.8%).

^1H NMR($CDCl_3$) : 1.44(s, 9H), 1.91-2.34(m, 5H), 3.73(m, 1H), 4.40-4.44(m, 2H), 4.65(m, 1H), 4.90(m, 1H), 5.49(m, 2H), 6.73(br-s, 1H), 7.27-7.30(m, 1H), 7.71-7.75(m, 2H), 8.16(s, 1H), 8.60-8.62(m, 1H)

MS : 406.21(ES+)

Example 5-5

tert-Butyl (1S)-2-[(2S)-2-cyano-1-pyrrolidinyl]-2-oxo-1-[[[(2-pyridinylmethylidene)amino]oxy]methyl]ethylcarbamate

To a slurry of tert-butyl (1S)-2-[(2S)-2-carbamoyl-1-pyrrolidinyl]-2-oxo-1-[[[(2-pyridinylmethylidene)amino]oxy]methyl]ethylcarbamate (120mg) obtained by Example 5-4 in tetrahydrofuran (2.4ml) were added triethylamine (0.13ml) and trifluoroacetic anhydride (TFAA, 0.084ml) dropwise at 5℃.

The reaction mixture was stirred at 5℃ for 30min,

then sat.$NaHCO_3$ was added, and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was purified with TLC (0.5mm X 1, $CHCl_3$:methanol=20:1) to give the target compound as a colorless oily amorphous (90mg, 78.5%).

^1H NMR($CDCl_3$) : 1.42(s, 9H), 2.17-2.30(m, 4H), 3.65-3.84(m, 2H), 4.37-4.42(m, 2H), 4.75-4.87(m, 2H), 5.30-5.37(m, 1H), 7.27-7.30(m, 1H), 7.65-7.85(m, 2H), 8.20(s, 1H), 8.59-8.62(m, 1H)

MS : 388.16(ES+)

Example 5-6

(2S)-1-[(2S)-2-Amino-3-[[(2-pyridinylmethylidene)amino]oxy]propanoyl]-2-cyanopyrrolidine dihydrochloride

tert-Butyl (1S)-2-[(2S)-2-cyano-1-pyrrolidinyl]-2-oxo-1-[[[(2-pyridinylmethylidene)amino]oxy]methyl]ethylcarbamate (70mg) obtained by Example 5-5 was dissolved in trifluoroacetic acid (TFA, 2ml) at room temperature, and the reaction mixture was stirred at room temperature for 30min.

After removal of the solvent in vacuo, the residual oil was dissolved in sat.$NaHCO_3$ and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and filtered. After removal of the solvent in vacuo, the residue was treated with 4N HCl-dioxane. After removal of the solvent in vacuo, the residue was triturated with diethylether, and the solvent was removed in vacuo. The target compound was obtained as a pale yellow amorphous powder (35mg, 53.8%).

^{1}H NMR(DMSO-d_6) : 1.95-2.32(m, 4H), 3.45-3.80(m, 3H), 4.51-4.62(m, 2H), 4.80-4.86(m, 1H), 7.50-7.55(m, 1H), 7.93(m, 2H), 8.27(s, 1H), 8.55-8.65(br-s, 2H), 8.65-8.70(m, 1H)

MS : 288.16(ES+), free 287.32

Example 6-1

tert-Butyl (1S)-2-[(2S)-2-carbamoyl-1-pyrrolidinyl]-1-[[[(1-methylethylidene)amino]oxy]methyl]-2-oxoethyl carbamate

tert-Butyl (1S)-2-[(2S)-2-carbamoyl-1-pyrrolidinyl]-1-[(aminooxy)methyl]-2-oxoethylcarbamate (300mg) was dissolved in acetone (10ml) at room temperature. The reaction mixture was set aside at room temperature for 10min.

The solvent was removed in vacuo, the residue was dissolved in ethyl acetate, washed with 1N HCl, sat.$NaHCO_3$, brine, and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was crystallized from diethylether-isopropylether to give the target compound as a white powder (150mg, 44.4%).

^{1}H NMR($CDCl_3$) : 1.44(s, 9H), 1.82(s, 3H), 1.84(s, 3H), 1.93-2.40(m, 4H), 3.61-3.73(m, 2H), 4.15-4.25(m, 2H), 4.63-4.70(m, 1H), 4.73-4.82(m, 1H), 5.20-5.28(m, 1H), 5.36-5.44(m, 1H), 6.90(br-s, 1H)

MS : 357.24(ES+)

Example 6-2

tert-Butyl (1S)-2-[(2S)-2-cyano-1-pyrrolidinyl]-1-[[[(1-methylethylidene)amino]oxy]methyl]-2-oxoethyl carbamate

To a solution of tert-butyl (1S)-2-[(2S)-2-carbamoyl-1-pyrrolidinyl]-1-[[[(1-methylethylidene)amino]oxy]methyl]-2-oxoethylcarbamate (145mg) obtained by Example 6-1 in tetrahydrofuran (3ml) was added triethylamine (0.17ml), then trifluoroacetic anhydride (TFAA, 0.115ml) dropwise at 5℃. The reaction mixture was stirred at 5℃ for 30min.

Sat.$NaHCO_3$ was added and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$. After removal of the solvent, the residue was dissolved in isopropylether, washed with 1N HCl, sat.$NaHCO_3$, brine, and dried over $MgSO_4$. After removal of the solvent in vacuo, the residue was crystallized from n-hexane. The crystals were collected by filtration, washed with n-hexane to give the target compound as a white powder (100mg, 72.6%).

^1H NMR($CDCl_3$) : 1.43(s, 9H), 1.85(s, 3H), 1.88(s, 3H), 2.12-2.30(m, 4H), 3.62-3.84(m, 2H), 4.18-4.21(m, 2H), 4.67-4.81(m, 2H), 5.30-5.37(m, 1H)

MS : 339.19(ES+)

Example 6-3

(2S)-1-[(2S)-2-Amino-3-[[(1-methylethylidene)amino]oxy]propanoyl]-2-cyanopyrrolidine trifluoroacetate

tert-Butyl (1S)-2-[(2S)-2-cyano-1-pyrrolidinyl]-1-[[[(1-methylethylidene)amino]oxy]methyl]-2-oxoethyl carbamate (50mg) obtained by Example 6-2 was dissolved in trifluoroacetic acid (1ml) at room temperature.

After 30min, the solvent was removed in vacuo, the residue was crystallized from isopropylether, collected by filtration, washed with isopropylether to give the target compound as a white powder (37.3mg, 71.7%).

^{1}H NMR(DMSO-d_6) : 1.82(s, 3H), 1.83(s, 3H), 1.94-2.30(m, 4H), 3.53-3.72(m, 2H), 4.21-4.34(m, 2H), 4.40-4.46(m, 1H), 4.80-4.85(m, 1H), 8.34(br-s, 2H)

MS : 239.18(ES+), free 238.29

Example 7-1

tert-Butyl 4-[(benzyloxy)imino]cyclohexylcarbamate

To a solution of tert-butyl 4-oxocyclohexylcarbamate (300 mg) and triethylamine (0.235ml) in methanol (5ml) at 0℃ was added O-benzylhydroxylamine hydrochloride (225mg) at the same temperature. The resulting mixture was warmed to room temperature and stirred for 2hrs.

The reaction was quenched with pouring H_2O. The aqueous layer was extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent was removed in vacuo. Recrystallization of the residue from hexane gave the target compound (259mg, 57.9%).

^{1}H NMR (in $CDCl_3$) : 1.23-1.45(m, 12H), 1.94-2.16(m, 3H), 2.18-2.24(m, 1H), 2.37-2.45(m, 1H), 3.11-3.23(m, 1H), 3.76(br-s, 1H), 4.43(br-s, 1H), 5.06(s, 2H), 7.29-7.35(m, 5H)

MS : 319.20 (ES+)

Example 7-2

4-Aminocyclohexanone O-benzyloxime

To a solution of tert-butyl 4-[(benzyloxy)imino]cyclohexylcarbamate (32mg) obtained by Example 7-1 in methanol (2ml) at room temperature was added 4N HCl in dioxane (5ml).

After stirring for 15min, the reaction was quenched with saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted three times with $CHCl_3$. The combined organic layer was washed with brine, dried over Na_2SO_4 and filtered. After removal of the solvent in vacuo, the target compound was given as colorless oil (26mg, about 100%).

Example 7-3

(2S)-1-[[[4-[(Benzyloxy)imino]cyclohexyl]amino]acetyl]-2-cyanopyrrolidine hydrochloride

To a solution of (2S)-1-(bromoacetyl)-2-pyrrolidinecarbonitrile(32mg) in tetrahydrofuran (2ml) at 0℃ was added a solution of 4-aminocyclohexanone O-benzyloxime (64mg) obtained by Example 7-2 in tetrahydrofuran (1ml) at that temperature

and stirred for 2hrs.

The reaction was quenched with pouring H_2O. The aqueous layer was extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The residue was purified with silica gel chromatography ($CHCl_3$:methanol=15:1). After removal of the solvent in vacuo, the residual oil was dissolved in methanol and 4N HCl-dioxane was added. After removal of the solvent, the residue was triturated by diethylether to give the target compound as a white powder (26mg, 45.1%).

^1H NMR (in DMSO-d_6) : 1.39-1.65(m, 2H), 1.80-2.42(m, 9H), 3.11-3.41(m, 3H), 3.41-3.57(m, 1H), 3.59-3.73(m, 1H), 3.94-4.19(m, 2H), 5.34(dd, J=4.5, 6.6Hz, 1H), 5.01(s, 2H), 7.29-7.41(m, 5H), 9.27(br-s, 1H)

MS : 355.22 (ES+)

Example 8-1

tert-Butyl 4-[(2-pyridinylmethoxy)imino]cyclohexyl-carbamate

To a solution of tert-butyl 4-oxocyclohexylcarbamate (100mg) in methanol (2ml) at room temperature was added O-(2-pyridinylmethyl)hydroxylamine (58mg) at that temperature.

After stirring for 10 min, the solvent was removed in vacuo. The resulting precipitate was triturated with diethylether to give the target compound as white powder (126mg, 84.1%).

^{1}H NMR (in $CDCl_3$) : 1.22-1.52(m, 11H), 1.96-2.28(m, 3H), 2.34-2.48(m, 1H), 3.15-3.30(m, 1H), 3.60-3.79(m, 1H), 4.36-4.55(m, 1H), 5.19(s, 2H), 7.15-7.22(m, 1H), 7.31-7.37(m, 1H), 7.64-7.72(m, 1H), 8.54-8.60(m, 1H)
MS : 320.18 (ES+)

Example 8-2
4-Aminocyclohexanone O-(2-pyridinylmethyl)oxime

Reaction was carried out in a manner similar to Example 7-2 using tert-butyl 4-[(2-pyridinylmethoxy)imino]cyclohexylcarbamate obtained by Example 8-1 to give 80mg of target compound (96.3%).

^{1}H NMR (in $CDCl_3$) : 1.21-1.55(m, 1H), 1.89-2.07(m, 2H), 2.07-2.23(m, 1H), 2.37-2.50(m, 1H), 2.91-3.06(m, 1H), 3.19-3.34(m, 1H), 3.71(s, 2H), 5.20(s, 2H), 7.12-7.24(m, 1H), 7.30-7.41(m, 1H), 7.62-7.73(m, 1H), 8.52-8.62(m, 1H)
MS : 220.17, 439.17 (ES+)

Example 8-3
(2S)-1-[[[4-[(2-Pyridinylmethoxy)imino]cyclohexyl]amino]acetyl]-2-cyanopyrrolidine hydrochloride

Reaction was carried out in a manner similar to Example 7-3 using 4-aminocyclohexanone O-(2-pyridinylmethyl)oxime obtained by Example 8-2 to give 17.2mg of target compound (22.7%).

^{1}H NMR (in DMSO-d_6) : 1.47-1.68(m, 2H), 1.87-2.40(m, 9H), 3.16(s, 2H), 3.20-3.38(m, 1H), 3.43-3.57(m, 1H), 3.61-3.73(m, 1H), 3.96-4.20(m, 2H), 4.81-4.90(m, 1H), 5.28(s, 2H), 7.69-7.82(m, 2H), 8.23-8.34(m, 1H), 8.72-8.79(m, 1H), 9.15-9.47(m, 2H)
MS 356.16 (ES+)

Example 9-1
tert-Butyl 4-[(3-pyridinylmethoxy)imino]cyclohexylcarbamate

Reaction was carried out in a manner similar to Example 8-1 using O-(3-pyridinylmethyl)hydroxylamine to give 180mg of target compound (60.1%).

^{1}H NMR (in $CDCl_3$) : 1.22-1.52(m, 11H), 1.91-2.16(m, 2H), 2.16-2.26(m, 1H), 2.32-2.46(m, 1H), 3.06-3.21(m, 1H), 3.56-3.78(m, 1H), 4.33-4.53(m, 1H), 5.06(s, 2H), 7.24-7.31(m, 1H), 7.63-7.70(m, 1H), 8.52-8.56(m, 1H), 8.58-8.61(m, 1H)
MS : 320.15 (ES+)

Example 9-2
4-Aminocyclohexanone O-(3-pyridinylmethyl)oxime

Reaction was carried out in a manner similar to Example 7-2 using tert-butyl 4-[(3-pyridinylmethoxy)imino]cyclohexylcarbamate obtained by Example 9-1 to give 120mg of target compound

(97.1%).

MS : 220.17 (ES+)

Example 9-3
(2S)-1-[[[4-[(3-Pyridinylmethoxy)imino]cyclohexyl]amino]acetyl]-2-cyanopyrrolidine hydrochloride

Reaction was carried out in a manner similar to Example 7-3 using 4-aminocyclohexanone O-(3-pyridinylmethyl)oxime obtained by Example 9-2 to give 49.1mg of target compound (37.3%).

^{1}H NMR (in DMSO-d_6) : 1.44-1.71(m, 2H), 1.86-2.42(m, 9H), 3.17-3.57(m, 2H), 3.57(s, 2H), 3.60-3.75(m, 1H), 3.94-4.21(m, 2H), 4.85(dd, J=4.2, 6.6Hz, 1H), 5.23(s, 2H), 8.00-8.09(m, 1H), 8.46-8.55(m, 1H), 8.85-8.92(m, 2H), 9.35(br-s, 1H), 9.46(br-s, 1H)
MS 356.19 (MS+)

Example 10-1
tert-Butyl 4-(methoxyimino)cyclohexylcarbamate hydrochloride

Reaction was carried out in a manner similar to Example 7-1 using methoxyamine hydrochloride to give 224mg of target compound (98.6%).

^{1}H NMR (in $CDCl_3$) : 1.20-1.53(m, 11H), 1.87-2.16(m, 4H), 2.16-2.27(m, 1H), 2.32-2.47(m, 1H), 2.99-3.17(m, 1H),

3.69(br-s, 1H), 3.82(s, 3H), 4.44(br-s, 1H)

MS : 243.17 (MS+)

Example 10-2

4-Aminocyclohexanone O-methyloxime

Reaction was carried out in a manner similar to Example 7-2 using tert-butyl 4-(methoxyimino)cyclohexylcarbamate hydrochloride obtained by Example 10-1 to give 105mg of target compound (79.8%).

^{1}H NMR (in $CDCl_3$) : 5.34(s, 2H), 7.26-7.30(m, 1H), 7.72-7.83(m, 6H), 8.55-8.56(m, 1H)

MS : 142.95 (ES+)

Example 10-3

(2S)-1-[[[4-(Methoxyimino)cyclohexyl]amino]acetyl]-2-cyanopyrrolidine hydrochloride

Reaction was carried out in a manner similar to Example 7-3 using 4-aminocyclohexanone O-methyloxime obtained by Example 10-2 to give 15mg of target compound (12.9%).

^{1}H NMR (in DMSO-d_6) : 1.37-1.68(m, 2H), 1.76-2.41(m, 9H), 3.04-3.15(m, 1H), 3.19-3.77(m, 7H), 3.94-4.21(m, 2H), 4.81-4.98(m, 1H), 9.26(br-s, 1H)

MS : 279.13 (ES+)

Example 11-1

tert-Butyl 4-(tert-butoxyimino)cyclohexylcarbamate

Reaction was carried out in a manner similar to Example 7-1 using tert-butoxyamine hydrochloride to give 264mg of target compound (99%).

MS : 285.25 (ES+)

Example 11-2

4-Aminocyclohexanone O-(tert-butyl)oxime

Reaction was carried out in a manner similar to Example 7-2 using tert-butyl 4-(tert-butoxyimino)cyclohexylcarbamate obtained by Example 11-1 to give 120mg of target compound (70.1%).

MS : 185.13 (ES+)

Example 11-3

(2S)-1-[[[4-(tert-Butoxyimino)cyclohexyl]amino]acetyl]-2-cyanopyrrolidine hydrochloride

Reaction was carried out in a manner similar to Example 7-3 using 4-aminocyclohexanone O-(tert-butyl)oxime obtained by Example 11-2 to give 24.3mg of target compound (21.1%).

^{1}H NMR (in DMSO-d_6) : 1.21(s, 9H), 1.35-1.61(m, 2H), 1.72-1.90(m, 1H), 1.92-2.44(m, 8H), 3.05-3.82(m, 6H), 3.96-4.22(m, 2H), 4.81-4.90(m, 1H), 9.20(br-s, 1H)

MS : 321.19 (ES+)

Example 12-1

tert-Butyl cis-4-[[[(5-cyano-2-pyridinyl)-methylidene]amino]oxy]cyclohexylcarbamate

Reaction was carried out in a manner similar to Example 3-1 using 5-cyano-2-pyridinecarboxaldehyde to give 311mg of target compound (34.7%).

^{1}H NMR (in $CDCl_3$) : 1.34-2.10(m, 17H), 3.56(br-s, 1H), 4.34-4.57(m, 2H), 7.90-8.00(m, 2H), 8.18(s, 1H), 8.35-8.89(m, 1H)

Example 12-2

cis-6-[[[(4-Aminocyclohexyl)oxy]imino]methyl]nicotinonitrile

Reaction was carried out in a manner similar to Example 3-2 using tert-butyl cis-4-[[[(5-cyano-2-pyridinyl)methylidene]amino]oxy]cyclohexylcarbamate obtained by Example 12-1 to give 265mg of target compound (99.4%).

^{1}H NMR (in DMSO-d_6) : 1.47-1.82(m, 6H), 1.99-2.14(m, 2H), 3.02-3.46(m, 2H), 4.43(br-s, 2H), 7.93-8.01(m, 1H), 8.26(s, 1H), 8.32-8.40(m, 6H), 9.05-9.10(m, 1H)
MS : 245.15 (ES+)

Example 12-3

cis-6-[[[[4-[[2-[(2S)-2-Cyano-1-pyrrolidinyl]-2-oxoethyl]amino]cyclohexyl]oxy]imino]methyl]nicotinonitrile

Reaction was carried out in a manner similar to Example 7-3 using cis-6-[[[(4-aminocyclohexyl)oxy]imino]methyl]nicotinonitrile obtained by Example 12-2 to give 68.1mg of target compound (38.9%).

^{1}H NMR (in $CDCl_3$) : 1.42-1.84(m, 8H), 2.00-2.37(m, 4H), 2.52-2.66(m, 1H), 3.43(s, 2H), 3.46-3.73(m, 2H), 4.37-4.48(m, 2H), 4.73-4.81(m, 1H), 7.26-7.30(m, 1H), 7.91-7.96(m, 2H), 8.18(s, 1H), 8.84-8.87(m, 1H)
MS : 381.19 (ES+)

Example 13-1
tert-Butyl trans-4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy]cyclohexylcarbamate

To a solution of tert-butyl cis-4-hydroxycyclohexylcarbamate (2g), hydroxyphthalimide (1.52g) and triphenylphosphine (2.68g) in tetrahydrofuran (50ml) at room temperature was added diisopropyl azodicarboxylate (DIAD, 2ml) and stirred at that temp for 2hrs.

The reaction was quenched by pouring H_2O. The aqueous layer was extracted with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and filtered. After removal of the solvent in vacuo, the residue was triturated diethylether and a few drop of

hexane to give the target compound as a white powder (3.3g, 98.6%).

MS : 359.18 (ES-)

Example 13-2

tert-Butyl trans-4-(aminooxy)cyclohexylcarbamate

A solution of tert-butyl trans-4-[(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)oxy] cyclohexylcarbamate (2g) obtained by Example 13-1 in ethanol (200ml) was warmed to 80℃. After the solution was turned clear, hydrazine monohydrate (9ml) was added at that temperature. The resulting mixture was heated at reflux for 1hr and then was cooled to room temperature.

The resulting precipitate was filtered off and washed with ethyl acetate and the filtrate was concentrated. The resulting mixture was diluted with 1N HCl and ethyl acetate, and the water layer was extracted with ethyl acetate. The aqueous layer was basified with solid $NaHCO_3$, saturated with NaCl and was extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over Na_2SO_4, and filtered. After removal of the solvent in vacuo, the target compound was given as an white powder (850mg, 39.7%).

^1H NMR (in $CDCl_3$) : 1.03-1.37(m, 4H), 1.44(s, 9H), 1.37-1.94(m, 4H), 1.94-2.13(m, 1H), 3.33-3.53(m, 2H), 4.37(br-s, 1H), 5.29(br-s, 2H)

MS : 231.19 (ES+)

Example 13-3

trans-tert-Butyl 4-[[(2-pyridinylmethylidene)amino]-oxy]cyclohexylcarbamate

To a solution of tert-butyl trans-4-(aminooxy)cyclohexylcarbamate (250mg) obtained by Example 13-2 in methanol(2ml) at room temperature was added 2-pyridinecarboxaldehyde at that temperature.

After stirring for 10 min, the solvent was removed in vacuo. The resulting precipitate was triturated with diisopropylether to give the target compound as white powder (250mg, 72.1%).

^{1}H NMR (in $CDCl_3$) : 1.14-1.34(m, 2H), 1.39-1.58(m, 11H), 2.00-2.25(m, 4H), 3.40-3.60(m, 1H), 4.12-4.27(m, 1H), 4.33-4.48(m, 1H), 7.21-7.29(m, 1H),7.64-7.80(m, 2H), 8.15(s, 1H), 8.59-8.61(m, 1H)

MS : 320.18 (ES+)

Example 13-4

2-Pyridinecarbaldehyde O-(trans-4-aminocyclohexyl)-oxime

Reaction was carried out in a manner similar to Example 7-2 using trans-tert-butyl 4-[[(2-pyridinylmethylidene)amino]oxy]cyclohexylcarbamate obtained by Example 13-3 to give 125mg of target compound (72.8%).

MS : 220.17 (ES+)

Example 13-5

trans-(2S)-1-[[[4-[[(2-Pyridinylmethylidene)amino]oxy]cyclohexyl]amino]acetyl]-2-cyanopyrrolidine dihydrochloride

Reaction was carried out in a manner similar to Example 7-3 using 2-pyridinecarbaldehyde O-(trans-4-aminocyclohexyl)oxime obtained by Example 13-4 to give 67.5mg of target compound (55.2%).

Example 14-1

tert-Butyl trans-4-[[(3-pyridinylmethylidene)amino]-oxy]cyclohexylcarbamate

Reaction was carried out in a manner similar to Example 13-3 using nicotinaldehyde to give 218mg of target compound (78.6%).

^{1}H NMR (in $CDCl_3$) : 1.36-1.34(m, 2H), 1.38-1.57(m, 11H), 1.98-2.27(m, 4H), 3.41-3.59(m, 1H), 4.04-4.21(m, 1H), 4.32-4.48(m, 1H), 7.22-7.35(m, 1H), 7.86-7.98(m, 1H), 8.06(s, 1H), 8.54-8.63(m, 1H), 8.70-8.76(m, 1H)

MS : 318.30 (ES-)

Example 14-2

Nicotinaldehyde O-(trans-4-aminocyclohexyl)oxime

Reaction was carried out in a manner similar to Example

7-2 using tert-butyl trans-4-[[(3-pyridinylmethylidene)amino]oxy]cyclohexylcarbamate obtained by Example 14-1 to give 155mg of target compound (about 100%).

Example 14-3

trans-(2S)-1-[[[4-[[(3-Pyridinylmethylidene)amino]oxy]cyclohexyl]amino]acetyl]-2-cyanopyrrolidine

Reaction was carried out in a manner similar to Example 7-3 using nicotinaldehyde O-(trans-4-aminocyclohexyl)oxime obtained by Example 14-2 to give 91.6mg of target compound (74.6%).

^{1}H NMR (in $CDCl_3$) : 1.16-1.55(m, 4H), 1.91-2.05(m, 2H), 2.06-2.38(m, 6H), 2.42-2.61(m, 1H), 3.36-3.80(m, 5H), 4.09-4.26(m, 1H), 4.72-4.83(m, 1H), 7.23-7.34(m, 1H), 7.91-8.00(m, 1H), 8.07(s, 1H), 8.56-8.61(m, 1H), 8.70-8.74(m, 1H)

MS : 356.19 (ES+)

Example 15-1

tert-Butyl trans-4-[[[1-(3-pyridinyl)ethylidene]-amino]oxy]cyclohexylcarbamate

Reaction was carried out in a manner similar to Example 13-3 using 3-acetylpyridine to give 166mg of target compound (57.3%).

^{1}H NMR (in $CDCl_3$) : 1.14-1.35(m, 2H), 1.39-1.59(m, 11H),

1.99-2.21(m, 4H), 2.23(s, 3H), 3.40-3.62(m, 1H), 4.06-4.22(m, 1H), 4.33-4.49(m, 1H), 7.23-7.32(m, 1H), 7.90-7.98(m, 1H), 8.54-8.59(m, 1H), 8.83-8.88(m, 1H)

MS : 334.23 (ES+)

Example 15-2

1-(3-Pyridinyl)ethanone O-(trans-4-aminocyclohexyl)-oxime

Reaction was carried out in a manner similar to Example 7-2 using tert-butyl trans-4-[[[1-(3-pyridinyl)ethylidene]amino]oxy]cyclohexylcarbamate obtained by Example 15-1 to give 110mg of target compound (94.7%).

Example 15-3

trans-(2S)-1-[[[4-[[[1-(3-Pyridinyl)ethylidene]amino]oxy]cyclohexyl]amino]acetyl]-2-cyanopyrrolidine dihydrochloride

Reaction was carried out in a manner similar to Example 7-3 using 1-(3-pyridinyl)ethanone O-(trans-4-aminocyclohexyl)oxime obtained by Example 15-2 to give 63mg of target compound (72%).

^{1}H NMR (in DMSO-d_6) : 1.34-2.42(m, 12H), 3.04-3.25(m, 1H), 3.33-3.96(m, 4H), 4.07-4.32(m, 2H), 4.90-4.99(m, 1H), 7.88-7.98(m, 1H), 8.54-8.66(m, 1H), 8.85-8.94(m, 1H), 9.08-9.14(m, 1H), 9.16-9.36(m, 1H)

MS : 370.24 (ES+)

Example 16-1

tert-Butyl trans-4-[[[(5-cyano-2-pyridinyl)-methylidene]amino]oxy]cyclohexylcarbamate

Reaction was carried out in a manner similar to Example 13-3 using 5-cyano-2-pyridinecarbaldehyde to give 190mg of target compound (62%).

^{1}H NMR (in $CDCl_3$) : 5.34(s, 2H), 7.26-7.30(m, 1H), 7.72-7.83(m, 6H), 8.55-8.56(m, 1H)

Example 16-2

trans-6-[[(4-Aminocyclohexyl)oxy]iminomethyl]nicotinonitrile

To tert-butyl trans-4-[[[(5-cyano-2-pyridinyl)-methylidene]amino]oxy]cyclohexylcarbamate (190mg) obtained by Example 16-1 was added trifluoroacetic acid (2ml) at room temperature and stirred for 2min.

The reaction was quenched with pouring a saturated aqueous solution of $NaHCO_3$. The aqueous layer was extracted three times with $CHCl_3$. The combined organic layer was washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo to gave the target compound as white powder (135mg, about 100%).

^{1}H NMR (in $CDCl_3$) : 1.10-1.63(m, 13H), 1.99-2.24(m, 4H), 3.39-3.58(m, 1H), 4.12-4.30(m, 1H), 4.30-4.49(m, 1H), 7.87-7.97(m, 2H), 8.12-8.19(m, 1H), 8.80-8.90(m, 1H)

Example 16-3

trans-6-[[[4-[[2-[(2S)-2-Cyano-1-pyrrolidinyl]-2-oxoethyl]amino]cyclohexyl]oxy]iminomethyl]nicotinonitrile dihydrochloride

Reaction was carried out in a manner similar to Example 7-3 using trans-6-[[(4-aminocyclohexyl)oxy]-iminomethyl]nicotinonitrile obtained by Example 16-2 to give 69mg of target compound (55.1%).

^{1}H NMR (in DMSO-d_6) : 0.948-2.29(m, 12H), 2.94-3.88(m, 5H), 3.92-4.26(m, 2H), 4.80-4.91(m, 1H), 7.92-7.99(m, 1H), 8.33-8.39(m, 1H), 9.01-9.26(m, 3H)

MS : 381.20 (ES+)

In order to illustrate the usefulness of the object Compound (I), the pharmacological test is carried out as shown in the following.

[A] Inhibition test of human plasma DPP-IV :

(i) Material and Method :

The effect of test compounds on DPP-IV activity in human plasma was evaluated with a modified version of the assay described by Hughes et al (Biochemistry, 38, pp11597-11603(1999)).

Briefly, 20μL of human plasma were mixed with 20 μL of 80mM $MgCl_2$ in assay buffer (25mM HEPES, 140mM NaCl, 1% RIA-grade BSA, pH7.8), and were incubated in a room temperature for 60min. Then the reaction was initiated

by the addition of both 20μL of test compounds and 20 μL of 0.2mM substrate (H-glycine-proline-AMC; AMC is 7-amino-4-methylcoumarine), they were dissolved in the assay buffer.

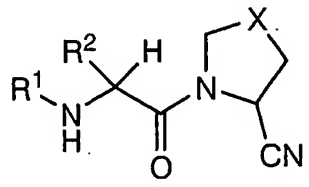
After 20min incubation in a room temperature (kept in the dark), fluorescence was measured (Excitation 380nm, Emission 460nm). A fluorescence-concentration curve of free AMC was obtained using AMC solution in the assay buffer with appropriate concentration. Plasma DPP-IV activities, with or without the test compounds, were expressed as the amount of product per minute per mL. The potency of the test compounds as DPP-IV inhibitor was expressed as IC_{50}.

Industrial Applicability

The Compound (I) or pharmaceutically acceptable salts thereof of the present invention have an inhibiting activity against DPP-IV. Therefore, the Compound (I) or pharmaceutically acceptable salts thereof are useful for treating or preventing disease mediated by DPP-IV, more particularly useful for treating or preventing altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus (IDDM and NIDDM), diabetic neuropathy, nephropathy, and secondary diseases in mammals or human caused by diabetes mellitus.

C L A I M S

1. A compound of the formula (I) or pharmaceutically acceptable salt thereof.

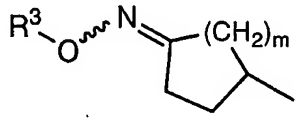


(I)

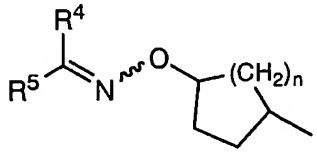
[wherein

X is CH_2, O or S,

R^1 is hydrogen, lower alkyl, the moiety represented by the formula:

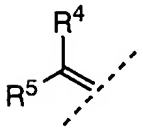


[wherein R^3 is lower alkyl, aryl (which may have 1 to 3 substituent(s) selected from the group described later), heteroaryl (which may have 1 to 3 substituent(s) selected from the group described later), aryl-(lower alkyl) (which may have 1 to 3 substituent(s) selected from the group described later on the aryl group), or heteroaryl-(lower alkyl) (which may have 1 to 3 substituent(s) selected from the group described later on the heteroaryl group), m is integer of 1 to 3], or the moiety represented by the formula:



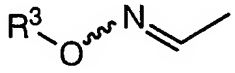
[wherein R^4 is hydrogen or lower alkyl, R^5 is lower alkyl, aryl (which may have 1 to 3 substituent(s) selected from the group described later), or heteroaryl (which may have 1 to 3 substituent(s) selected from the group

described later), or the partial structure:

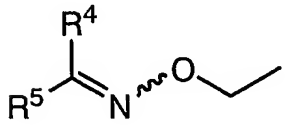


may form cycloalkyl, n is integer of 1 to 3],

R^2 is hydrogen, the moiety represented by the formula:



[wherein R^3 represents the same definition defined above], or the moiety represented by the formula:

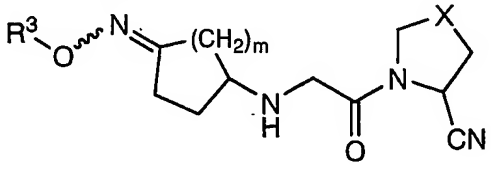


[wherein R^4 and R^5 represent the same definition defined above],

the substituent(s) is(are) selected from the group consisting of lower alkyl, lower alkoxy, halogen, cyano, nitro, amino and hydroxy,

provided that both of R^1 and R^2 are not hydrogen at the same time; and either R^1 and R^2 is hydrogen, or when R^1 is lower alkyl, R^2 is not hydrogen.]

2. A compound of the formula (II) or pharmaceutically acceptable salt thereof.



(II)

[wherein

X is CH_2, O or S,

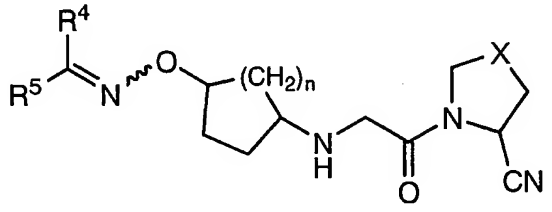
R^3 is lower alkyl, aryl (which may have 1 to 3

substituent(s) selected from the group described later), heteroaryl (which may have 1 to 3 substituent(s) selected from the group described later), aryl-(lower alkyl) (which may have 1 to 3 substituent(s) selected from the group described later on the aryl group), or heteroaryl-(lower alkyl) (which may have 1 to 3 substituent(s) selected from the group described later on the heteroaryl group),

m is integer of 1 to 3

the substituent(s) is(are) selected from the group consisting of lower alkyl, halogen, cyano, nitro, amino and hydroxy]

3. A compound of the formula (III) or pharmaceutically acceptable salt thereof.



(III)

[wherein

X is CH_2, O or S,

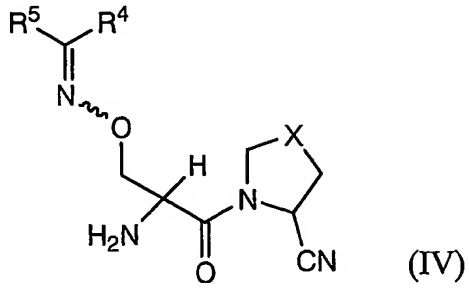
R^4 is hydrogen or lower alkyl,

R^5 is lower alkyl, aryl (which may have 1 to 3 substituent(s) selected from the group described later), or heteroaryl (which may have 1 to 3 substituent(s) selected from the group described later),

n is integer of 1 to 3

the substituent(s) is(are) selected from the group consisting of lower alkyl, halogen, cyano, nitro, amino and hydroxy]

4. A compound of the formula (IV) or pharmaceutically acceptable salt thereof.



(IV)

[wherein

X is CH_2, O or S,

R^4 is hydrogen or lower alkyl,

R^5 is lower alkyl, aryl (which may have 1 to 3 substituent(s) selected from the group described later), or heteroaryl (which may have 1 to 3 substituent(s) selected from the group described later),

the substituent(s) is(are) selected from the group consisting of lower alkyl, halogen, cyano, nitro, amino and hydroxy]

5. A medicament comprising the compound according to any one of Claim 1 to 4 as an active ingredient.

6. A pharmaceutical composition comprising the compound according to any one of Claim 1 to 4 as an active ingredient, in association with a pharmaceutically acceptable carrier or excipient.

7. An inhibitor of DPP-IV consisting of the compound according to any one of Claim 1 to 4.

8. A method for treatment and/or prevention of the medical conditions mediated by DPP-IV which comprises administering an effective amount of the compound according to any one of Claim 1 to 4 to human beings or animals.

9. The method according to Claim 8, wherein the medical conditions mediated by DPP-IV is altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus, diabetic neuropathy, nephropathy, or secondary diseases in mammals caused by diabetes mellitus.

10. The method according to Claim 8, wherein the medical conditions mediated by DPP-IV is NIDDM.

11. The compound according to any one of Claim 1 to 4 for use in the treatment and/or prevention of the medical conditions mediated by DPP-IV in human beings or animals.

12. The compound according to Claim 11, wherein the medical conditions mediated by DPP-IV is altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus, diabetic neuropathy, nephropathy, or secondary diseases in mammals caused by diabetes mellitus.

13. The compound according to Claim 11, wherein the medical conditions mediated by DPP-IV is NIDDM.

14. Use of the compound according to any one of Claim

1 to 4 for the manufacture of a medicament for treatment and/or prevention of the medical conditions mediated by DPP-IV in human beings or animals.

15. The use according to Claim 14, wherein the medical conditions mediated by DPP-IV is altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus, diabetic neuropathy, nephropathy, or secondary diseases in mammals caused by diabetes mellitus.

16. The use according to Claim 14, wherein the medical conditions mediated by DPP-IV is NIDDM.

17. A commercial package comprising the pharmaceutical composition containing the compound identified in any one of Claim 1 to 4 and a written matter associated therewith, wherein the written matter states that the compound can or should be used for preventing and/or treating the medical conditions mediated by DPP-IV.

18. The commercial package according to Claim 17, wherein the medical conditions mediated by DPP-IV is altered glucose tolerance, glucosuria, hyperlipidemia, metabolic acidosis, diabetes mellitus, diabetic neuropathy, nephropathy, or secondary diseases in mammals caused by diabetes mellitus.

19. The commercial package according to Claim 17, wherein the medical conditions mediated by DPP-IV is NIDDM.